RESEARCH ARTICLE

Optimizing Orphan Drug Rucaparib Transdermal Patches for Ovarian Cancer: A Design Expert-Based Strategy for Prolonged Drug Release

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ABSTRACT

This study aimed to develop and characterize transdermal patches for rucaparib using a Box-Behnken design (BBD), evaluating drug permeation at 8, 12, and 24 hours, with optimization through Design Expert software. The patches were formulated with HPMC K15, ethyl cellulose, and PVP K30. The physicochemical properties and drug infusion were tested and characterized. The transdermal patches developed in this study were found to be soft and flexible, indicating good handling properties and potential for comfortable application. The patches demonstrated sustained drug release, extending beyond 24 hours, which is crucial for preserving consistent beneficial levels of rucaparib in the systemic circulation. The optimal formulation, as identified through the BBD using Design Expert software, included HPMC K15 (100 mg), ethyl cellulose (200 mg), and PVP K30 (40 mg). This combination effectively facilitated prolonged drug penetration while keeping the flexibility and integrity of the patches. The study concludes that the formulated transdermal patches using HPMC K15, ethyl cellulose, and PVP K30 offer an effective means for prolonged delivery of DPZ and MMZ. The optimized patches support sustained discharge for a prolonged time, which can improve patient compliance and therapeutic outcomes in treating ovarian cancer. The use of a systematic design approach, such as the BBD, proved beneficial in optimizing the formulation parameters, ensuring the development of high-quality transdermal patches with desirable properties for clinical application.

Keywords: Box Behnken Design, Drug permeation, Orphan drug, Ovarian cancer, patch.

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INTRODUCTION

Orphan drugs are pharmaceutical agents developed specifically to treat rare diseases, which are conditions affecting a small percentage of the population. These diseases, often called orphan diseases, usually lack sufficient market potential to attract research and development investments from pharmaceutical companies without government incentives.[1] The development of orphan drugs is crucial because many rare diseases are severe, chronic, and life-threatening, yet they often lack effective treatments.[2] Orphan drugs offer hope to patients with rare diseases and contribute to medical advancements and innovations. Focusing on rare conditions can lead to a better understanding of disease mechanisms, potentially benefiting more common diseases.[3]

Rucaparib is a potent inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, particularly PARP-1, PARP-2, and PARP-3. These enzymes play a crucial role in DNA repair mechanisms, particularly in the repair of single-strand breaks.[4] By inhibiting PARP, rucaparib induces synthetic lethality in cancer cells deficient in homologous recombination repair (HRR) pathways, such as those with $BRCA_1$ or $BRCA_2$ mutations.[5] This inhibition leads to the buildup of DNA injury, eventually producing cancer cell death. Rucaparib is primarily used in the treatment of ovarian cancer, particularly in patients with deleterious BRCA mutations or who have shown a positive response to platinum-based chemotherapy. It has been approved for use as both a monotherapy and a maintenance therapy, demonstrating significant efficacy

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in prolonging progression-free survival in these patient populations. Additionally, rucaparib has shown promise in treating other cancers with HRR deficiencies, including certain types of breast and prostate cancers.[6] The drug is administered orally, offering convenience compared to some other cancer therapies. Common side effects of rucaparib include nausea, fatigue, anemia, and elevated liver enzymes.[7] More severe but less common side effects can include myelodysplastic syndrome and acute myeloid leukemia, necessitating regular monitoring of patients during treatment.[8] Transdermal patches are a novel drug delivery system designed to deliver medications through the skin directly into the bloodstream, offering several advantages over traditional oral or injectable routes. These patches improve patient compliance due to their ease of use and painless application and provide controlled release of medication over an extended period, ensuring steady therapeutic levels and reducing side effects. By bypassing the gastrointestinal tract, transdermal delivery avoids issues such as gastric irritation and first-pass metabolism, enhancing the bioavailability of certain medications.[9] The consistent drug levels maintained by transdermal patches reduce the risk of side effects from fluctuating concentrations and offer convenience and discretion. Advancements in materials and technologies continue to expand the range of drugs deliverable transdermally, improve drug permeation efficiency, and incorporate technologies like microneedles and iontophoresis to enhance delivery. Transdermal patches represent a significant advancement in drug delivery systems, providing controlled, sustained drug release, improving patient compliance, and bypassing the gastrointestinal tract, making them essential in modern therapeutic strategies. As research and technology advance, their applications and effectiveness are expected to expand, further enhancing their role in healthcare.[10]

This study aimed to develop and thoroughly characterize transdermal patches for rucaparib by employing a Box-Behnken Design (BBD) methodology. The research involved evaluating the drug permeation through the patches at different time points: 8, 12, and 24 hours. Optimization of the formulation parameters was performed using Design Expert software to ensure the effectiveness and efficiency of the patches. The transdermal patches were formulated with a combination of HPMC K15, ethyl cellulose, and PVP K30, which were selected for their potential to enhance the drug delivery and stability of the patches. The comprehensive characterization included assessing the physicochemical properties of the patches, such as thickness, moisture content, and drug release profile, to ensure they met the desired specifications for therapeutic efficacy.

MATERIAL AND METHODS

Materials

Rucaparib was gifted from Zydus Cadila, Ahmedabad, India. Merck supplied HPMC K15, ethyl cellulose, PVP K30, methanol, and polyethylene glycol-400. The cellulose acetate membrane necessary for the patches was sourced from Chemtech India. All other chemicals and materials used were of AR grade.

Making of the Patch

Rucaparib patches were prepared using the solvent casting method with HPMC K15, ethyl cellulose, and PVP K30 dissolved in methanol (25 mL). The mixture was enthused for 30 minutes with a magnetic stirrer, and then added polyethylene glycol-400 (1-mL). Rucaparib was then combined into the solution under incessant stirring. The resulting polymeric solution with rucaparib (450 mg) was poured into a petri dish and allowed to dry at room temperature for 6 hours. After drying, the patches were cut into 1x1 cm squares, wrapped in aluminum foil, and stored in desiccators until further use.[11-13] A BBD was employed to evaluate 15 different blends using Design Expert Software (Version 13) to analyze Rucaparib permeation at various intervals (DP@8h, DP@12h, and DP@24h) (Table 1).

Compatibility Observations

The samples were meticulously prepared by thoroughly blending with finely ground potassium bromide (KBr) to ensure homogeneity. This mixture was then pressed into transparent pellets using a hydraulic press. The formed pellets were subjected to detailed analysis using a Fourier-transform infrared (FTIR) spectrophotometer, which scanned the samples across a wide spectral range, from 4000 to 400 cm^{-1}.

Appeal

The evaluation of all transdermal patches (TDP) involved a comprehensive assessment of several key physical attributes. First, each patch's color, clarity, flexibility, and smoothness were meticulously inspected using a magnifying lens. This careful inspection ensured that even minor imperfections were identified, allowing for a thorough quality assessment. Additionally, the thickness of each patch was precisely measured using a screw gauge. This instrument provided accurate and consistent data collection, which is critical for ensuring uniformity across the samples. These evaluations are crucial in determining the physical attributes and quality

Table 1: Different independent variables and the dependent variables used in the investigation

Independent variables	*Levels*		
	Low	*Medium*	*High*
X_1= HPMC K15 (mg)	100	125	150
X_2= Ethyl cellulose (mg)	100	150	200
X_3= PVP K30 (mg)	30	40	50
Distorted values	-1	0	+1
Responses observed	Conditions		
Y_1= DP@8h (Rucaparib drug permeation at 8 hours)	Maximize		
Y_2= DP@8h (Rucaparib drug permeation at 16 hours)	Maximize		
Y_3= DP@8h (Rucaparib drug permeation at 24 hours)	Maximize		

parameters of the TDP. The detailed assessment of color, clarity, flexibility, and smoothness, combined with precise thickness measurements, provides essential information about the patches. This information is vital for their further characterization and potential application in drug delivery systems, ensuring that the patches meet the necessary standards for effective and safe use.

Weight Variation

Each transdermal patch was individually weighed to obtain precise measurements. To assess the mean weight, the weights of five individual patches were summed and then divided by five, providing an average weight for the batch. This process of determining the mean weight is critical for ensuring uniformity across the patches, as consistent weight indicates a consistent composition.[14,15] Uniform weight is essential to prevent any issues during packaging and to maintain the reliability and consistency of the transdermal patches. This quality control measure ensures that each patch delivers the intended dosage effectively, which is crucial for the therapeutic efficacy and safety of the drug delivery system. By maintaining stringent control over the weight of the patches, manufacturers can ensure that each unit meets the required standards, providing confidence in the product's performance and reliability.

Flexibility of the Patches

The flexibility of each transdermal patch was assessed by carefully folding them along the same plane until they cracked. This method provided a tangible measure of the patches' ability to withstand bending without breaking, reflecting their durability during handling and application. Patches that exhibited greater resistance to cracking demonstrated higher flexibility, which is essential for their ability to conform to the contours of the skin during application while maintaining structural integrity. This evaluation is crucial in determining the overall quality and usability of the patches.[16] High flexibility ensures that the patches remain intact and effective during wear, contributing to patient comfort and adherence to treatment. By ensuring that the patches can endure the stresses of everyday use without compromising their performance, this assessment helps guarantee that the transdermal delivery system will be both reliable and user-friendly.

Mechanical Strength

To ensure the transdermal patches (TDPs) were securely supported within the patch holder, adhesive tape was affixed to one end of the patch. A small pin was then inserted into the tape at the opposite end to maintain the patch's straight alignment and prevent deformation during expansion. To measure the tensile strength of the TDPs, a pulley system was employed. One end of a thread was fixed to the small pin on the patch, and the thread was passed over a pulley. Weights were gradually added to the other end of the thread. As the weights increased, a pointer traced the movement of the thread on graph paper.[17] The breaking force of the patch was determined by the weight at which the patch ruptured under tension. This method provided a precise assessment of the patch's mechanical resilience, ensuring that it could withstand the typical forces encountered during handling and application. By measuring the tensile strength, the evaluation validated the durability of the TDPs for practical use, confirming their capability to endure real-world conditions without compromising their structural integrity. This thorough testing process is essential to guarantee the reliability and effectiveness of the transdermal delivery system in delivering the intended therapeutic benefits to patients.[18]

Assessing the Moisture in the Patches

The patches were placed in desiccators containing calcium chloride ($CaCl_2$) to maintain a low-humidity environment. This setup facilitated the absorption of moisture from the surroundings, establishing a dry atmosphere around the samples. The procedure involved periodically weighing the patches at predetermined intervals to monitor their moisture content accurately. Initially, the patches were weighed while wet, including any moisture content present. The patches then underwent a drying process to eliminate moisture. This involved keeping the patches in the desiccators until no further weight loss was observed in consecutive weighings, indicating that the patches had stabilized and were completely dry.[19] The difference between the initial wet weight and the stabilized dry weight of the patches represented the amount of moisture initially present in the samples. This meticulous drying process ensured an accurate determination of the patches' moisture content, which is crucial for preserving their stability and quality during storage and use. Accurately measuring and controlling the moisture content of the patches is essential for maintaining their structural integrity and efficacy.[20] Excess moisture can affect the patches' adhesive properties, drug release rates, and overall performance. Therefore, this procedure is vital for ensuring the patches remain effective and reliable throughout their shelf life and during patient use (E.q.1).

$$\text{Moisture content } \frac{\text{Initial weight - Final weight}}{\text{Final weight}} X100 - - - - (1)$$

Drug Content

The TDPs were cut into 1x1 cm^2 pieces and immersed in 100 mL of phosphate buffer contained in a beaker. To facilitate the release of the drug from the patches into the solution, the mixture was agitated. After the agitation period, the solution was filtered through Whatman filter paper to remove any particulate matter. The filtrate was then analyzed using a UV spectrophotometer. The absorbance of the solution was measured at 355 nm, a specific wavelength for Rucaparib.[21,22] By comparing these absorbance measurements to a calibration curve, the concentration of rucaparib in the filtrate could be determined. This process provided valuable data on the amount of drug released from the patches and allowed for the assessment of the drug release kinetics and efficiency. By understanding how effectively and at what rate rucaparib is released, the performance of the transdermal patches can be

evaluated, which is crucial for ensuring the therapeutic efficacy and proper dosing of the medication.

Drug Diffusion Study

A Franz diffusion cell system was employed to evaluate the permeation of drugs through a cellophane membrane, which serves as a model for the skin barrier. In this setup, a phosphate buffer solution with a pH of 7.4 was used as the medium, mimicking physiological conditions. The diffusion of the drug through the membrane was monitored using spectrophotometric analysis. The diffusion cell system was maintained at a constant temperature of 32°C, provided by a water bath, to simulate body temperature and ensure consistent experimental conditions. Sampling from the diffusion cell was performed at predetermined intervals: 8, 12, and 24 hours. These intervals allowed for the measurement of drug permeation kinetics over time. By analyzing the samples at these specific time points, data on the release profile and efficiency of the transdermal patches could be gathered. This process provided critical information on how effectively the drug is released and permeates through the cellophane membrane, which is essential for assessing the performance of the transdermal patches and their potential effectiveness in drug delivery.[23]

RESULTS

The FTIR spectra of rucaparib, both in its pure form and when combined with various excipients, were thoroughly analyzed. The distinguishing peaks of rucaparib were identified and compared between the pure drug and the drug-excipient mixtures. The characteristic peaks of rucaparib, including those corresponding to its functional groups, such as the C=O stretch, N-H bend, and aromatic C-H stretch, remained unchanged when the drug was combined with different excipients. This observation suggests that there were no significant interactions or chemical reactions between rucaparib and the selected excipients (Figures 1 and 2).

The prepared transdermal patches were observed to be thin, translucent, and free from air bubbles and gaps, indicating high-quality fabrication. The thickness of the patches was uniformly consistent across different formulations, ranging from 0.34 ± 0.02 to 0.48 ± 0.03 mm. Among them, TDP-6 was identified as the thinnest formulation. The patches demonstrated consistent weight uniformity, with weights

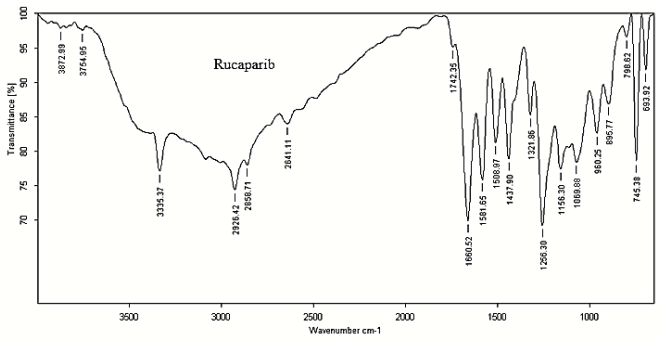

Figure 1: FTIR spectra of rucaparib pure

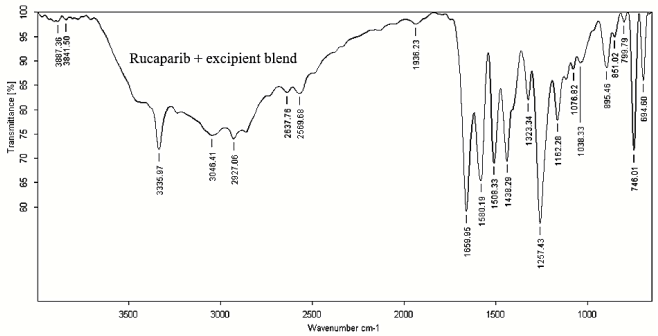

Figure 2: FTIR spectra of rucaparib with its excipients

ranging from 621.23 ± 3.01 mg for TDP-2 to 632.04 ± 2.65 mg for TDP-3. Minor variations in weight were observed due to the different proportions of ingredients used in each formulation. Flexibility tests indicated that all patches exhibited excellent flexibility, with folding endurance exceeding 180 folds for all formulations. Notably, TDP-3 demonstrated the highest folding endurance, breaking at 195 ± 5 folds, likely due to its higher ethyl cellulose (EC) content and minimal hydroxypropyl methylcellulose (HPMC) K15 content. The moisture content in the patches was minimal, not exceeding 3.31 ± 0.02% in any formulation. The tensile strength of the patches was commendable, with TDP-3 exhibiting the highest tensile strength at 0.697 ± 0.01 mg/cm²/h. This could be attributed to its lesser HPMC K15 and higher EC content. All patches demonstrated good drug retention, holding more than 90% of rucaparib (Table 2).

In-vitro rucaparib permeation

Observations were made to assess the sustained release properties of the various transdermal patches. The results revealed consistent rucaparib permeation across all patches, confirming their ability to maintain a steady discharge of the drug. Notably, formulation TDP-3, which included HPMC K15 (100 mg), PVP K30 (40 mg), and ethyl cellulose (200 mg), exhibited superior Rucaparib permeation (93.6 ± 1.25%) compared to the other formulations (Figure 3).

Model Accuracy and Precision

The analysis of rucaparib permeation at 8, 12, and 24 hours using Design Expert software produced a fit summary (Table 3). The software's evaluation helps optimize the model by eliminating insignificant terms while preserving the model's hierarchy. This method ensures that the final model is concise and accurately describes the data. The resulting equation for the responses is as follows:

$$DP@8h=+34.1-0.3625A+3.02B-0.5375C+0.225AB+0.3AC+0.275\ BC1.60A^2+0.025B^2-0.5C^2$$

$$DP@16h=+67.89-0.531A+5.07B-0.77C-0.3875AB0.35AC+0.1BC+2.81A^2+0.96B^2+0.299C^2$$

$$DP@24h=+84.9-0.3488A+8.54B-0.536C+0.32AB+0.302AC+0.1BC+2.31A^2\ -2.29B^2-0.66C^2$$

Table 2: Physicochemical of TDPs

Trial	*Appeal*	*Thickness (mm)*	*UW (mg)*	*FE*	*MC (%)*	*TS (mg/cm²/h)*	*DPZ content (%)*
TDP-1	Good	0.45 ± 0.02	630.74 ± 1.37	186 ± 6	2.95 ± 0.09	0.654 ± 0.01	91.38 ± 3.26
TDP-2	Good	0.42 ± 0.02	621.23 ± 3.01	191 ± 2	2.75 ± 0.04	0.676 ± 0.02	94.53 ± 5.68
TDP-3	Good	0.45 ± 0.01	632.04 ± 2.65	195 ± 5	2.35 ± 0.04	0.697 ± 0.01	97.32 ± 3.36
TDP-4	Good	0.44 ± 0.02	628.74 ± 1.75	182 ± 2	2.84 ± 0.01	0.679 ± 0.02	94.67 ± 1.48
TDP-5	Good	0.46 ± 0.03	624.28 ± 0.64	185 ± 3	3.26 ± 0.02	0.651 ± 0.01	95.51 ± 2.58
TDP-6	Good	0.34 ± 0.02	627.74 ± 1.25	186 ± 6	2.84 ± 0.05	0.669 ± 0.03	96.84 ± 0.08
TDP-7	Good	0.40 ± 0.02	629.84 ± 3.61	183 ± 1	3.31 ± 0.02	0.659 ± 0.03	94.62 ± 1.59
TDP-8	Good	0.39 ± 0.01	623.53 ± 2.62	185 ± 4	2.79 ± 0.01	0.675 ± 0.01	92.64 ± 2.27
TDP-9	Good	0.41 ± 0.02	624.03 ± 5.02	194 ± 1	3.30 ± 0.02	0.669 ± 0.02	94.21 ± 2.85
TDP-10	Good	0.42 ± 0.01	625.41 ± 3.34	173 ± 3	3.23 ± 0.03	0.678 ± 0.01	93.87 ± 1.64
TDP-11	Good	0.44 ± 0.03	631.82 ± 2.25	187 ± 4	2.68 ± 0.01	0.659 ± 0.01	91.23 ± 1.95
TDP-12	Good	0.46 ± 0.02	629.07 ± 4.10	198 ± 2	3.19 ± 0.02	0.657 ± 0.01	92.63 ± 5.16
TDP-13	Good	0.44 ± 0.01	628.47 ± 2.75	189 ± 3	2.97 ± 0.03	0.658 ± 0.02	93.33 ± 3.84

UW- Uniformity of weight; FE- Folding endurance; MC- Moisture content; TS- Tensile strength; values in mean ± SD; trials (n)=3

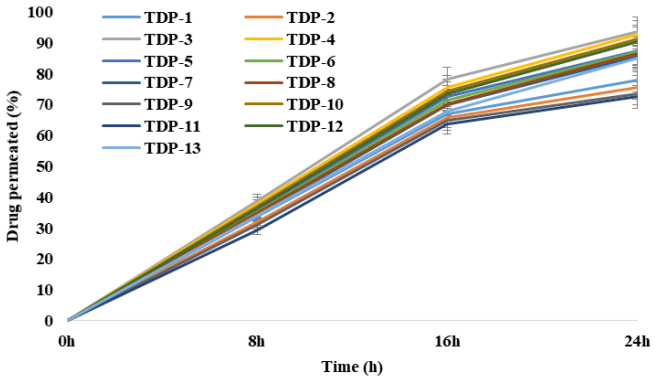

Figure 3: *In-vitro* drug permeation from rucaparib patches

The responses for Rucaparib permeation at 8, 12, and 24 hours were analyzed using Design Expert software. The data points in Table 3 closely matched the graphs, showing a strong correlation between the residuals and the predicted values. This close agreement between the residuals and predicted appraisals indicates the model's accuracy and reliability.

Model Significance

The model F-values of 25.09, 43.46, and 71.9 indicate that the models are highly significant. The probabilities of these F-values occurring due to noise are only 1.13, 0.51, and 0.24%, respectively. The associated *p-values* below 0.05 highlight significant model terms, specifically:

First Model: Significant terms include A, B, and C.

Second Model: Significant terms include A, B, C, AB, B^2, and C^2.

Third Model: Significant terms include A, B, C, A^2, B^2, and C^2.

Residual and Model Influence

Residuals versus predicted values for the responses were illustrated in Figure 4 (A, C, and E), showing the residuals *versus* run. Cook's distance, depicted in Figure 4 (B, D, and F), represented the influence of individual data points on the model. These figures highlight the impact of input factors on the response.

Table 3: Fit Summary of the dependent variables

Response 1: DP@8h			
Source	*Sequential p-value*	*Adjusted R²*	*Predicted R²*
Linear	0.0003	0.8180	0.7043
2FI	0.9233	0.7465	0.3159
Quadratic	0.0547	0.9476	
Response 2: DP@12h			
Linear	< 0.0001	0.8683	0.8096
2FI	0.9559	0.8121	0.5926
Quadratic	0.0382	0.9696	
Response 3: DP@24h			
Linear	< 0.0001	0.9001	0.8349
2FI	0.9901	0.8528	0.5898
Quadratic	0.0261	0.9815	

Contour plots illustrating the permeation of rucaparib at various time points are shown in Figure 5 (A) DP@8h, C) DP@16h, and E) DP@24h). Additionally, 3D response surface plots for these outputs are displayed in Figure 5 (B) DP@8h, D) DP@16h, and F) DP@24h), providing a more comprehensive visualization of the drug permeation dynamics.

DISCUSSION

The FTIR spectra of the rucaparib-excipient mixtures showed preserved distinguishing peaks of rucaparib, indicating maintained structural integrity. This lack of new peaks or significant shifts confirms no chemical interaction between the drug and excipients, ensuring the drug's efficacy and stability. This compatibility is crucial for developing effective and stable transdermal patches, as it allows the excipients to aid

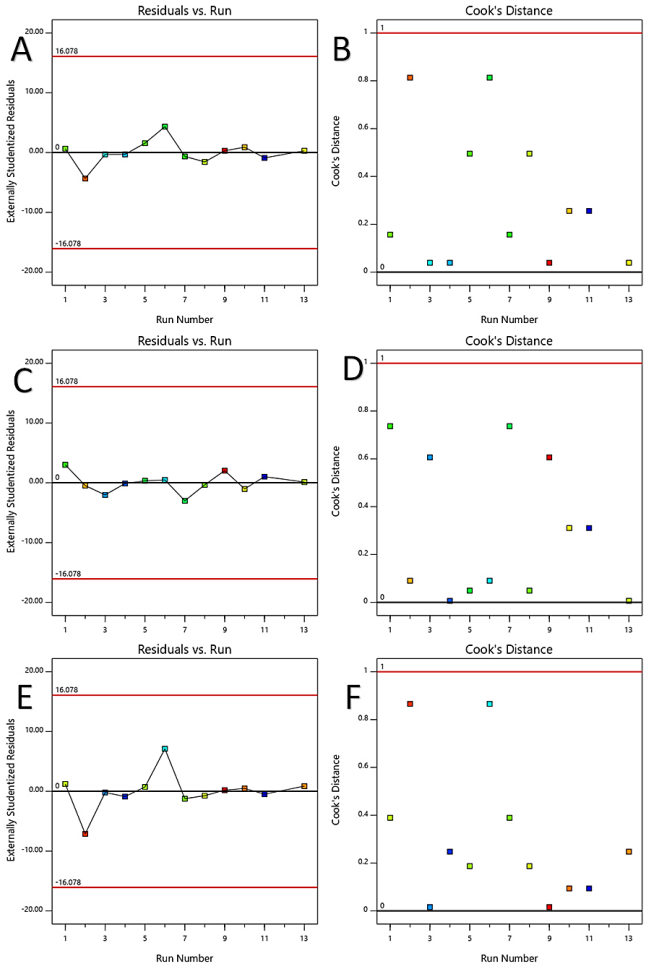

Figure 4: Residual *vs*. predicted (A, C, and E), Cook's distance (B, D, and F) indicating the influence of independent variables on the response

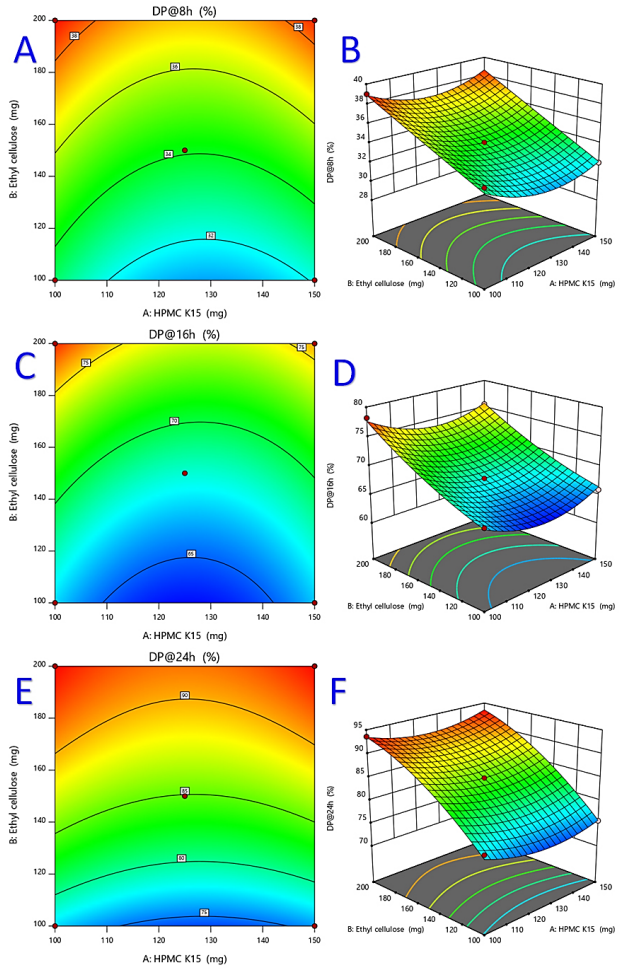

Figure 5: Contour (A, C, and E) and 3D (B, D, and F) plots for the outputs for the responses

in drug delivery without compromising the drug's therapeutic properties.

The evaluation of the prepared transdermal patches revealed their high quality and suitability for drug delivery applications. The patches were thin, translucent, and free from air bubbles and gaps, indicating a high-quality fabrication process. They exhibited uniform thickness and consistent weight, essential for consistent drug dosing. Minor weight variations were expected due to different ingredient proportions. The patches showed excellent flexibility and high folding endurance, with TDP-3 demonstrating superior flexibility due to higher EC content. The minimal moisture content is crucial for maintaining stability and preventing microbial growth. The commendable tensile strength ensures the patches withstand mechanical stresses, with TDP-3 showing the highest tensile strength. High drug retention in all patches ensures effective therapeutic action.[24]

The *in-vitro* permeation studies assessed the sustained release properties of the transdermal patches, focusing on the consistent release of rucaparib over time. All formulations achieved controlled and sustained drug release profiles. Among them, TDP-3 showed the highest permeation rate at 93.6 ± 1.25%. This superior performance is attributed to the optimal combination of HPMC K15, PVP K30, and ethyl cellulose. HPMC K15's gel-forming properties, PVP K30's solubilizing effect, and EC's hydrophobic barrier synergistically enhanced rucaparib's release. These findings highlight the importance of selecting the right excipient combination to achieve the desired drug release profile. The superior permeation of TDP-3 suggests its significant potential for effective rucaparib delivery through the skin, making it a promising candidate for further development in transdermal drug delivery systems.

The Design Expert software analysis of responses at 8, 12, and 24 hours produced a fit summary that refined the model by removing insignificant terms while preserving its structure. This led to a concise and effective model for describing the data. The close correlation between residuals and predicted values confirms the model's accuracy, capturing variability and allowing reliable predictions of rucaparib permeation. The model's robust performance highlights its utility in optimizing transdermal patch formulations and predicting drug release kinetics. The results affirm that Design Expert is an effective

tool for model optimization, ensuring accurate predictions of drug release profiles.[25-30]

The Design Expert software analysis of Rucaparib permeation data shows that the models are highly significant, with F-values of 25.09, 43.46, and 71.9, indicating effective explanation of data variability and very low noise probabilities (1.13, 0.51, and 0.24%). The *p-values* below 0.05 confirm the significance of the model terms. For the first model (8 hours), terms A, B, and C are significant. In the second model (12 hours), terms A, B, C, AB, B^2, and C^2 are crucial, reflecting linear, interaction, and quadratic effects. The third model (24 hours) highlights A, B, C, A^2, B^2, and C^2 as significant, emphasizing the importance of these variables and their quadratic effects. These findings offer valuable insights into optimizing transdermal patch formulations for enhanced rucaparib delivery. The models' high significance and minimal noise validate their effectiveness in predicting and optimizing drug permeation.[31-37]

The residuals *versus* predicted values plots provide a visual assessment of the model's accuracy. The distribution of residuals around the zero line suggests that the model predictions are unbiased and that the errors are randomly distributed. This indicates that the model has adequately captured the underlying relationship between the variables and the responses. Cook's distance plots offer insight into the influence of individual data points on the model. High Cook's distance values indicate data points that have a substantial impact on the model's predictions. Identifying these influential points is crucial for understanding the robustness of the model and ensuring that it is not unduly affected by outliers or anomalous data. Together, the residuals versus predicted values and Cook's distance plots highlight the reliability of the model in capturing the effects of input factors on rucaparib permeation. The residuals' random distribution supports the model's validity, while Cook's distance identifies key data points influencing the model. These analyses confirm that the model is both accurate and robust, providing confidence in its predictions and its utility for optimizing transdermal patch formulations.

The contour plots provide a two-dimensional view of rucaparib permeation at different time points, helping to identify the relationship between the formulation variables and the drug release. These plots highlight regions of optimal permeation, facilitating the identification of the best formulation conditions for sustained drug release. The response surface plots offer a more detailed visualization of the drug permeation dynamics, depicting how rucaparib release changes over time as a function of the formulation variables. The three-dimensional perspective allows for a clearer understanding of the interactions between variables and their combined effects on drug permeation. The DP@8h, DP@16h, and DP@24h plots in contour and 3D illustrate the sustained release profile of rucaparib, emphasizing how different formulations can influence the drug release rate over time. These visual tools are crucial for optimizing transdermal patch formulations, as they provide a comprehensive understanding of the factors that drive drug permeation and help pinpoint the most effective combination of ingredients and conditions for achieving desired therapeutic outcomes. By analyzing these contour and 3D response surface plots, researchers can effectively tailor the formulation to ensure consistent and efficient drug delivery, ultimately enhancing the efficacy and reliability of the transdermal patches.

CONCLUSION

This study successfully developed and characterized transdermal patches for rucaparib, an orphan drug, using a Box-Behnken design (BBD) and optimization via Design Expert software. The formulation included HPMC K15, ethyl cellulose, and PVP K30, which were evaluated for their physicochemical properties and drug release profiles. The resulting patches exhibited desirable characteristics such as softness, flexibility, and the capability for comfortable application. Notably, the patches demonstrated sustained rucaparib release beyond 24 hours, which is essential for maintaining effective therapeutic levels in systemic circulation. The optimal formulation, identified through BBD analysis, consisted of 100 mg HPMC K15, 200 mg ethyl cellulose, and 40 mg PVP K30. This combination proved to be highly effective in ensuring prolonged drug permeation while maintaining the integrity and flexibility of the patches. The optimized patches not only support sustained drug release but also enhance patient compliance and therapeutic efficacy in the treatment of ovarian cancer. The study underscores the utility of systematic design approaches like BBD for optimizing formulation parameters. The successful development of these high-quality transdermal patches highlights their potential for improved patient outcomes and provides a robust platform for further clinical applications.

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